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Insulin-Like Growth Factor-I, Insulin-Like Growth Factor-Binding Proteins, and Gonadotropins in the Hypothalamic-Pituitary Axis and Serum of Nutrient-Restricted Ewes[1]

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ABSTRACT

Body condition scores (BCS) of ovariectomized estradiol-treated ewes were controlled to examine effects of suboptimum BCS on insulin-like growth factor (IGF)-I, IGF-binding proteins (IGFBPs), and LH in the anterior pituitary gland, hypophyseal stalk-median eminence (SME), and circulation. Serum LH increased in ewes with BCS (1 = emaciated, 9 = obese) $>$ 3 (HIGH-BCS), but not in ewes with BCS $\leq$ 3 (LOW-BCS), after onset of the breeding season. Concentrations of LH and LHβ subunits in anterior pituitary glands were lower in LOW-BCS than in HIGH-BCS ewes. Serum IGF-I was lower in LOW-BCS than in HIGH-BCS ewes but did not differ in SME or anterior pituitary glands. In serum, the 44-kDa IGFBP-3 and 24-kDa IGFBP-4 were lower in LOW-BCS than in HIGH-BCS ewes. In anterior pituitary glands, IGFBP-2 tended to be higher in LOW-BCS than in HIGH-BCS ewes. In the SME, IGFBP-2, -3, and -5 were lower in LOW-BCS than in HIGH-BCS ewes. Low body condition may inhibit the increased secretion of LH associated with the onset of the breeding season by altering relative amounts of IGFBPs within the hypothalamic-pituitary axis.

INTRODUCTION

The influence of nutrition on reproduction has been extensively investigated and, as a result, it is generally concluded that release of GnRH is suppressed in undernourished animals [1–4]. Glucose has been implicated as a regulator of the release of GnRH [1, 5–7]. A threshold circulating concentration of glucose appears to be required for reproduction, with deleterious effects on reproduction occurring below this threshold [1]. Discrete mechanisms, however, that selectively regulate neural utilization of glucose have not been identified. In vitro studies demonstrated that insulin-like peptides participate in the control of brain energy metabolism [8] and may be involved with hypothalamic control of reproduction [9]. Because insulin-like growth factor-I (IGF-I) has an integral function in intermediary metabolism, Schillo [10] suggested that IGF-I may act as an important mediator of the effects of nutrition on reproduction in cattle and sheep.

IGF-I functions as an endocrine, paracrine, and/or autocrine regulator of cellular processes, including uptake of glucose [11, 12]. Synthesis of IGF-I occurs in many tissues including brain, hypothalamus, and pituitary gland [13, 14]. IGF-I and IGF-binding proteins (IGFBPs) are present in the anterior pituitary gland, hypothalamus, and serum of cattle and sheep [5, 15]. Serum and anterior pituitary gland concentrations of IGF-I in cattle remained unchanged during the estrous cycle [15]. Relative amounts of IGFBPs, however, in the anterior pituitary gland varied in association with progesterone during the estrous cycle in cattle [15] and were regulated by estradiol in both the anterior pituitary gland and hypophyseal stalk median eminence (SME) in sheep [16].

Chronic restriction of dietary energy decreased serum concentrations of IGF-I in beef cows, and IGF-I increased in association with onset of reproductive function [17–19]. Therefore, it was hypothesized that IGF-I and/or IGFBPs mediate release of GnRH and LH by exerting endocrine, paracrine, or autocrine actions at the hypothalamus and pituitary gland. Furthermore, IGF-I activity may be modified by interactions of serum and/or tissue concentrations of IGF-I with serum and/or tissue concentrations of stimulatory and inhibitory IGFBPs. The current experiment was conducted to determine how suboptimal body condition concomitantly suppresses circulating concentrations of LH and influences IGF-I and IGFBPs in the anterior pituitary gland, hypophyseal SME, and circulation of ewes.

MATERIALS AND METHODS

Mature, ovariectomized white-faced Western range ewes in moderate body condition (body condition score [BCS] 5.9 ± 0.2; 1 = emaciated, 9 = obese [20]) were weighed (73.7 ± 1.13 kg) and randomly allotted to 2 dietary groups. These diets provided 100% of National Research Council Requirements [21] for protein, vitamins, and minerals, ad libitum access to water and trace mineral salt blocks, and 100% or 60% of National Research Council (NRC) [21] requirements for net energy. On July 1 (Day 1), diets were initiated and all animals received s.c. a 10-mm silicone elastomer implant containing crystalline estradiol-17β (Sigma, St. Louis, MO). These implants were designed to maintain basal circulating concentrations of estradiol near 5 pg/ml [2, 22, 23]. This estradiol treatment inhibits secretion of LH during the anestrous season but not during the breeding season [24] in ewes with BCS $>$ 3 [2]. Hence, animals were retrospectively assigned to HIGH-BCS (BCS $>$ 3; n = 6) or LOW-BCS (BCS $\leq$ 3; n = 8) groups at the end

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of the experiment to determine effects of suboptimal nutrition on traits measured.

Blood samples were collected before feeding at 12-min intervals for 6 h on Days 7 (July 7), 30, 60, and 75. Days 60 and 75 were near (September 1) or after (September 15) onset of the breeding season in comparable intact ewes maintained at the University of Wyoming. Blood was allowed to clot overnight at 4°C; then serum was separated by centrifugation (1500 × *g* for 20 min) and stored at −20°C until analysis.

Ewes were slaughtered on Day 80, and an additional blood sample, pituitary glands, and SMEs were collected as described previously [25]. Anterior pituitary glands were trimmed of connective tissue and bisected midsagittally. Tissues were wrapped in foil, frozen in liquid nitrogen, and stored at −70°C.

Total carcass energy was calculated as described previously [20]. Briefly, kidney, pelvic, and heart fat were collected and weighed. Viscera were weighed, emptied of feed and fecal material, and reweighed. All muscle and fat tissue was stripped from the skeleton, separated, and weighed. Lipid, dry matter, ash [26], and total protein (kg) content of each carcass were calculated [20]. Total fat (kg) and total protein (kg) were multiplied by 9.45 and 5.65, respectively, to calculate total energy (kcal) of carcasses [27]. All animal studies were approved by the University of Wyoming Animal Care Committee.

Analysis of Hormones

Serum concentrations of LH were determined in duplicate by RIA [28] using antisera described by Adams et al. [29] at an initial dilution of 1:100 000. Radioiodinated LH (LER 1268-1; NIDDK) was used as labeled antigen, and concentrations of LH were expressed as nanograms of NIH-LH-S18 standard preparation. Sensitivity of the assay was 0.4 ng/ml. Interassay and intraassay CV were 12.3% and 13.0%, respectively. Mean and basal concentrations of LH, pulse frequency/6 h, and pulse amplitude were determined. The criterion used to identify a pulse was an increase in serum concentration of LH two standard deviations above basal concentration of LH followed by a corresponding decrease in LH. Concentrations of LH in anterior pituitary gland homogenates (diluted 1:10 000 to 1:100 000 in PBS-0.1% gel) were measured in a single assay with an intraassay CV of 4.7%.

Pituitary concentrations of FSH were determined as described by Bolt [30] using ovine FSH (NIDDK-oFSH-I-SIAFP-21) as radioiodinated antigen, ovine FSH (NIDDK-oFSH-RP-1) as standard, and NIDDK-anti-oFSH-1 at an initial dilution of 1:80 000. Concentrations of FSH in anterior pituitary homogenates (1:1000 and 1:10 000 in PBS-0.1% gel) were determined in a single assay with an intraassay CV of 5.5%.

Concentrations of IGF-I in serum (first sample collected on Days 7–75 and at slaughter) and tissue were determined in duplicate as described previously [5, 16, 31]. Recombinant human IGF-I (DRG010; Bachem, Torrance, CA) was used as the radioiodinated antigen and standard. Antiserum UB3–189 (National Hormone and Pituitary Program, NIDDK) was used at an initial dilution of 1:2000. Sensitivity of the assay was 1.95 ng/ml. Intraassay and interassay CV were 10.2% and 15.1%, respectively. Concentrations of IGF-I in anterior pituitary glands and SME were measured [5] in a single assay with an intraassay CV of 4.6%.

Analysis and Identification of IGFBPs

Relative amounts of IGFBPs in tissue and serum samples were analyzed by one-dimensional SDS-PAGE [32] and ligand blotting [33, 34] as described previously [5, 16].

Identity of IGFBP-2, -4, and -5 in serum and tissues was confirmed by immunoprecipitation as described previously [16, 35]. On the basis of the similarity in molecular masses of IGFBPs identified in cattle [15, 36], the IGFBP detected as a 40/44-kDa doublet in serum and a 36/40-kDa doublet in tissues was presumed to be IGFBP-3. Aliquots of SME homogenates were analyzed for hemoglobin (cat. #525-A; Sigma Chemical Co.) to evaluate potential contamination from serum due to vascularity near the SME. No detectable quantities of hemoglobin were present.

Northern and Dot Blots

Total RNA was extracted from half of each anterior pituitary using TRI-Reagent (Molecular Research Company, Cincinnati, OH). Purity of RNA was determined by measuring the A_{260}:A_{280} ratio.

Relative amounts of mRNA for α, LHβ, and FSHβ subunits were determined by dot blot analysis and hybridization with radioactive cDNA probes encoding bovine α subunit [37], bovine LHβ subunit [38], or FSHβ subunit [39]. Hybridization and wash conditions were similar to those described previously [40]. After hybridization, relative amounts of mRNA for each of the subunits (expressed as arbitrary densitometric units; ADU) were determined by phosphoimagery (Molecular Dynamics, Sunnyvale, CA). Relative abundance of gonadotropin subunit mRNA in individual pituitaries was divided by relative amounts of cyclophilin mRNA (ADU gonadotropin/ADU cyclophilin) [41] to normalize loading of RNA.

Statistical Analysis

Serum concentrations of LH, IGF-I, and relative amounts of IGFBPs in serum were analyzed by least-squares analysis for a split-plot design using the General Linear Models of the Statistical Analysis System [42]. Effects of BCS (LOW-BCS vs. HIGH-BCS) were determined using animal within BCS as the error term. Date and BCS × date interactions were evaluated in the split plot using residual mean square as the error term. When date or BCS × date interactions were significant ($p < 0.05$), means were compared using Fisher's protected LSD procedure [43]. Effects of BCS on tissue concentrations of hormones, IGFBPs, and relative amounts of mRNA for gonadotropins subunits at slaughter were analyzed by one-way ANOVA [42]. Pearson's correlations among hormones, IGFBPs, and IGF-I in tissues and serum collected at slaughter were also determined [42].

RESULTS

Average BCS determined on Days 75 and 80 were 4.2 ± 0.2 and 2.5 ± 0.2 for HIGH-BCS and LOW-BCS ewes, respectively. Carcasses of LOW-BCS ewes had less ($p < 0.05$) total carcass energy (54.5 ± 9.7 kcal) than did those of HIGH-BCS ewes (143.2 ± 10.3 kcal).

Mean serum concentrations of LH were influenced ($p < 0.05$) by a BCS × day interaction (Fig. 1). Mean serum concentrations of LH increased ($p < 0.05$) at onset of the breeding season (Days 60 and 75) in HIGH-BCS ewes but remained suppressed ($p < 0.05$) in LOW-BCS ewes. Frequency of LH pulses (0.9 ± 0.3 and 1.1 ± 0.3 pulses/6 h

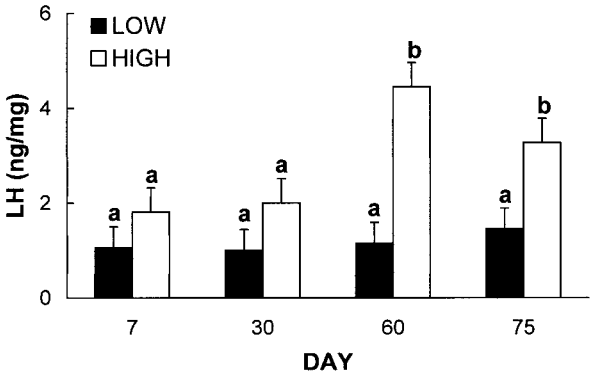

FIG. 1. Mean serum concentrations of LH in LOW-BCS and HIGH-BCS ewes on Days 7, 30, 60, and 75. Values are least-squares means ± SEM for 8 LOW-BCS and 6 HIGH-BCS ewes. Means with different letters differ according to group and (or) time ($p < 0.05$).

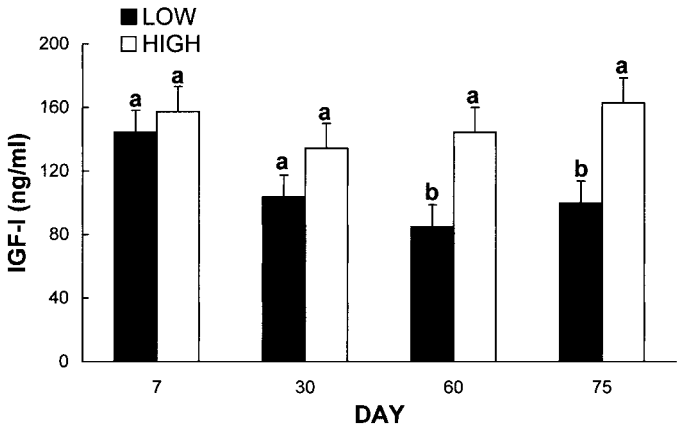

FIG. 3. Mean serum concentrations of IGF-I in LOW-BCS and HIGH-BCS ewes at Days 7, 30, 60, and 75. Values are least-squares means ± SEM for 8 LOW-BCS and 6 HIGH-BCS ewes. Means with different letters differ ($p < 0.05$) for LOW-BCS and HIGH-BCS ewes at each respective day.

for LOW-BCS and HIGH-BCS ewes, respectively) did not differ ($p > 0.1$) due to BCS grouping or days. Amplitude of LH pulses, however, tended to be greater ($p < 0.07$) in HIGH-BCS than in LOW-BCS ewes (3.6 ± 0.8 vs. 1.6 ± 0.7 ng/mL), but date and BCS × date interactions were not significant ($p > 0.1$).

Concentrations of LH (ng/g) in the anterior pituitary gland and relative amounts of mRNA for the LHβ subunit were lower ($p < 0.05$) in LOW-BCS than in HIGH-BCS ewes (Fig. 2). In contrast, pituitary gland concentrations of FSH (10.2 ± 2.2 vs. 14.0 ± 2.3 ng/g) and relative amounts of mRNA for the FSHβ subunit (1.38 ± 0.32 vs. 0.82 ± 0.38) and α subunit (10.5 ± 1.8 vs. 7.4 ± 1.4) did not differ ($p > 0.1$) for HIGH-BCS and LOW-BCS ewes, respectively.

Serum concentrations of IGF-I (ng/ml) were influenced by BCS ($p < 0.05$) and tended ($p < 0.08$) to be influenced by date (Fig. 3). Circulating concentrations of IGF-I at slaughter differed ($p < 0.05$) for HIGH-BCS (141.6 ± 12.1) and LOW-BCS (99.3 ± 9.5) ewes; however, concentrations of IGF-I (ng/g tissue) in anterior pituitary gland (37.8 ± 3.1 vs. 35.6 ± 2.7) and SME (25.3 ± 3.6 vs. 24.2 ± 3.1) tissues were similar ($p > 0.1$) in HIGH-BCS and LOW-BCS ewes, respectively.

Six IGFBPs of different molecular masses were detected in serum. On the basis of immunoprecipitation in this and previous studies [15, 16, 35, 36], these proteins were identified as a 29-kDa IGFBP (presumably IGFBP-1; [44]), IGFBP-2 (34 kDa), IGFBP-3 (40 kDa and 44 kDa), and IGFBP-4 (24 kDa and 28 kDa). Relative quantities of IGFBP-1, the 40-kDa form of IGFBP-3, and the 28-kDa form of IGFBP-4 were not ($p > 0.1$) influenced by BCS, date, or BCS × date interactions. Quantities of IGFBP-2 increased by Day 75 ($p < 0.05$; Table 1) but were not influenced by BCS or BCS × date interactions. The 44-kDa form of IGFBP-3 ($p < 0.01$) and the 24-kDa form of IGFBP-4 ($p < 0.01$) were higher in HIGH-BCS than in LOW-BCS ewes but were not influenced ($p > 0.1$) by date or BCS × date interactions.

Four IGFBPs of different molecular masses were detected in anterior pituitary glands and SMEs (Table 2). On the basis of immunoprecipitation in this and previous studies [15, 16, 35, 36], these proteins were identified as IGFBP-2 (32 kDa), 36- and 40-kDa forms of IGFBP-3, and IGFBP-5 (29 kDa). LOW-BCS ewes tended ($p < 0.1$) to have greater amounts of IGFBP-2 in anterior pituitary glands than did HIGH-BCS ewes. No differences ($p > 0.1$), however, were detected in relative amounts of IGFBP-3 and IGFBP-5 in anterior pituitary glands from LOW-BCS and

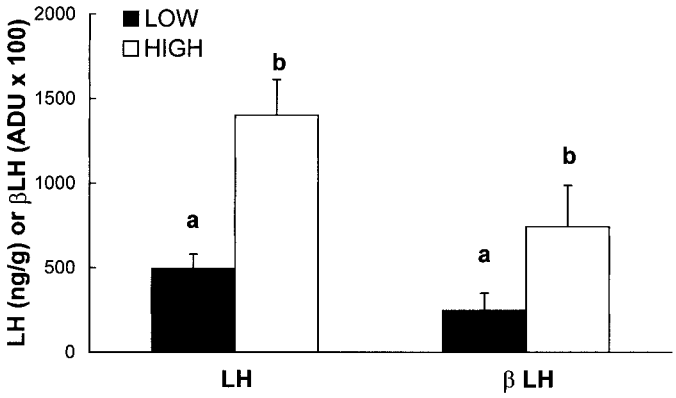

FIG. 2. Anterior pituitary concentrations of LH (ng/ml) and relative amounts of LHβ subunit (βLH) mRNA expressed as ADU × 100 in LOW-BCS and HIGH-BCS ewes. Values are least-squares means ± SEM for 8 LOW-BCS and 6 HIGH-BCS ewes. Relative amounts of mRNA were normalized to relative amounts of cyclophilin mRNA. Means with different letters differ ($p < 0.05$) for LOW-BCS and HIGH-BCS ewes.

TABLE 1. Relative abundance of IGFBP-2, 44-kDa IGFBP-3, and 24-kDa IGFBP-4 in serum of LOW-BCS and HIGH-BCS ewes on Days 7, 30, 60 and 75 (least-squares means ± SEM arbitrary densitometer units).

IGFBP	Day	Low (n = 8)	High (n = 6)
IGFBP-2	7	1.33 ± 0.12[c]	1.17 ± 0.14[c]
	30	1.53 ± 0.12[c,d]	1.51 ± 0.14[c,d]
	60	1.62 ± 0.12[c,d]	1.54 ± 0.14[c,d]
	75	1.71 ± 0.12[d]	1.66 ± 0.14[d]
44-kDa IGFBP-3	7	2.46 ± 0.17[a]	3.22 ± 0.19[b]
	30	2.67 ± 0.17[a]	3.70 ± 0.19[b]
	60	2.55 ± 0.17[a]	3.25 ± 0.19[b]
	75	2.61 ± 0.17[a]	3.60 ± 0.19[b]
24-kDa IGFBP-4	7	0.09 ± 0.02[a]	0.20 ± 0.02[b]
	30	0.08 ± 0.02[a]	0.16 ± 0.02[b]
	60	0.08 ± 0.02[a]	0.20 ± 0.02[b]
	75	0.08 ± 0.02[a]	0.16 ± 0.02[b]

[a,b] Means within rows with different letters differ ($p < 0.05$); date and date × group effects did not differ ($p > 0.05$).
[c,d] Means within columns with different numbers differ ($p < 0.05$); group and group × date effects did not differ ($p > 0.05$).

TABLE 2. Relative abundance of IGFBPs in anterior pituitary glands (AP) and SME of LOW-BCS and HIGH-BCS ewes (least-squares means ± SEM arbitrary densitometer units).

Tissue	IGFBP	Low (n = 8)	High (n = 6)
AP	BP-2 (32 kDa)	3.96 ± 0.39[a]	2.64 ± 0.45[b]
	BP-3 (36 kDa)	0.52 ± 0.05	0.55 ± 0.06
	BP-3 (40 kDa)	0.34 ± 0.04	0.39 ± 0.04
	BP-5 (29 kDa)	1.18 ± 0.15	1.03 ± 0.17
SME	BP-2 (32 kDa)	3.10 ± 0.57[c]	5.28 ± 0.65[d]
	BP-3 (36kDa)	1.57 ± 0.06[e]	1.99 ± 0.07[f]
	BP-3 (40 kDa)	1.53 ± 0.06[e]	1.89 ± 0.07[f]
	BP-5 (20 kDa)	1.61 ± 0.07[e]	2.10 ± 0.08[f]

[a,b] Means with different superscripts tend ($p < 0.10$) to differ.
[c,d] Means with different superscripts differ ($p < 0.05$).
[e,f] Means with different superscripts differ ($p < 0.01$).

HIGH-BCS ewes. In contrast, SME homogenates from HIGH-BCS ewes had greater ($p < 0.05$) relative amounts of IGFBP-2, 36- and 40-kDa forms of IGFBP-3 ($p < 0.01$), and IGFBP-5 ($p < 0.01$) than did LOW-BCS ewes.

Serum concentrations of LH were positively correlated with total carcass energy ($r = 0.84$; $p < 0.01$) and anterior pituitary gland concentrations of LH ($r = 0.79$; $p < 0.01$) but not ($p > 0.1$) with serum concentrations of IGF-I or IGFBPs. In anterior pituitary glands, correlations were not ($p > 0.1$) observed among components of the IGF-system (IGF-I and IGFBPs) with total carcass energy, mean serum concentrations of LH, or anterior pituitary gland concentrations of LH and FSH. In the SME, however, total carcass energy was positively correlated with IGFBP-2 ($r = 0.81$; $p < 0.05$), IGFBP-3 (36 and 40 kDa; $r = 0.93$ and 0.84, respectively; $p < 0.01$;) and IGFBP-5 ($r = 0.91$; $p < 0.01$). Mean serum concentrations of LH were positively correlated ($p < 0.05$) with IGFBP-2 ($r = 0.60$), IGFBP-3 (40 kDa; $r = 0.55$), and IGFBP-5 ($r = 0.67$) in the SME. Anterior pituitary LH was also positively correlated ($p < 0.05$) with IGFBP-3 (40 kDa; $r = 0.55$) and IGFBP-5 ($r = 0.62$) in the SME.

DISCUSSION

Similar to the case in previous studies [2, 45], secretion and synthesis of LH was diminished in ewes with body condition scores of ≤ 3. That this subjective measure accurately predicts body composition is supported by previous studies [20, 46] and the corresponding amounts of carcass energy calculated for ewes in the present study.

In contrast to the findings of Kile and coworkers [2], pituitary concentrations of FSH and mRNA for the FSHβ and α subunits did not differ between LOW-BCS and HIGH-BCS ewes in the current study. This discrepancy between studies is probably due to larger loss (31.6%) of body weight in ewes reported by Kile et al. [2] compared to an approximately 16% loss in body weight in the current study. Beckett et al. [47], however, found that pituitary concentrations of FSH and mRNA for FSHβ subunit increased with moderate and severe nutrient restriction of lambs. Thus, effects of nutrient restriction on tissue concentrations and synthesis of FSH are not resolved.

Ovariectomized estradiol-treated ewes have been used extensively to determine mechanisms that regulate seasonality of reproduction. Onset of the breeding season is characterized by an ''escape from negative feedback actions of estradiol'' [22–24] and a resulting increased secretion of LH. Using this model, it was demonstrated further that there was no increased secretion of LH associated with onset of the breeding season if ewes were in poor body condition (i.e., BCS ≤ 3; [2]). It was also demonstrated that estradiol increased serum concentrations of IGF-I and evoked divergent effects on IGFBPs [16]. Therefore, the relationship between circulating concentrations of IGF-I and LH at the onset of the breeding season in HIGH-BCS ewes from the present study supports the concept that IGF-I may participate in the regulation of reproduction by nutrition in ewes.

Concentrations of IGF-I in the anterior pituitary gland or SME did not differ between LOW-BCS and HIGH-BCS ewes. Changes, however, in relative amounts of IGFBPs in each tissue were detected. These results are similar to those of Funston et al. [15], who reported that amounts of IGFBPs, but not IGF-I, change in the bovine pituitary during the estrous cycle. Because IGF-I is involved with release of LH [48] and synthesis of GnRH [49], altered amounts of IGFBPs in anterior pituitary gland and/or SME tissue could modify actions of IGF-I in the absence of actual changes in concentrations of IGF-I.

IGFBPs are important regulators of IGF-I activity [50]. They are generally considered to inhibit the activity of endogenous IGF-I, although individual IGFBPs may potentiate effects of IGF-I or independently affect cellular processes [12, 51]. Regulation of IGFBPs is tissue-specific and is affected by numerous factors including IGF-I, growth hormone, and estradiol [12, 16]. Concomitant decreases in circulating quantities of IGF-I and IGFBP-3 in response to nutritional restriction of sheep and cattle have been reported [44, 52, 53]. Because IGFBP-3 serves as a major binding protein for storage of IGF-I [54], this may simply reflect decreased amounts of IGF-I and a decreased need for carrier proteins. Current results provide evidence that the two forms of IGFBP-3 in serum differ in their response to restriction of dietary energy. The 44-kDa form of IGFBP-3 decreased after 7 days of feeding an energy-deficient diet, whereas no change was detected in the 40-kDa form. Decreased quantities of the 24-kDa form of IGFBP-4 in serum of LOW-BCS ewes may also reflect decreased IGF-I activity in serum. This IGFBP, which acts primarily to inhibit IGF activity, would be expected to change in association with IGF-I to counteract hypoglycemic effects of IGF-I [55].

Differential changes noted in relative concentrations of IGFBPs among serum, anterior pituitary gland, and SME samples, as well as differences in apparent molecular masses (i.e., kDa) of individual IGFBPs, supports the concept of localized production and regulation of IGFBPs. Relative amounts of IGFBP-2 in the anterior pituitary gland tended to be greater in LOW-BCS than in HIGH-BCS ewes while other IGFBPs did not differ. This may be indicative of a net inhibition of IGF-I activity by IGFBP-2 [12]. Clapper et al. [16] found that estradiol increased amounts of mRNA for IGFBP-2 in anterior pituitaries of ewes and suppressed secretion of LH.

Few studies exist that describe changes in the IGF-I system within the SME. In this tissue, IGFBP-2, IGFBP-3, and IGFBP-5 were detected. Amounts of IGFBPs detected in the SME were positively correlated with total carcass energy, providing a potentially important insight into mechanisms by which suboptimal nutrition may alter hypothalamic control of hypophyseal reproductive function. Although identification of precise roles of these IGFBPs in the SME awaits further investigation, estradiol has been shown to influence these proteins in the SME [16].

In summary, undernutrition in ewes differentially altered the IGF-I system in the anterior pituitary gland and SME, resulting in tissue-specific changes in relative amounts of IGFBPs. In addition, there were decreased serum concentrations of IGF-I and relative amounts of IGFBP-3 (44 kDa) and IGFBP-4 (24 kDa) in LOW-BCS ewes. These results provide evidence that components of the IGF-I system have the potential to function via endocrine, paracrine, and/or autocrine mechanisms to modulate reproductive processes during periods of undernutrition. It is hypothesized that functions of the IGF-system are manifested through changes in relative amounts of IGFBPs within the hypothalamic-pituitary axis. Identification of mechanisms that regulate production and actions of individual IGFBPs, however, requires further study.

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